REMARKS

Entry of this Amendment is proper under 37 C.F.R. § 1.116 because the Amendment places the application in condition for allowance for the reasons discussed herein; does not raise any new issue requiring further search and/or consideration because the amendments amplify issues previously discussed throughout prosecution; and places the application in better form for an appeal should an appeal be necessary. The Amendment is necessary and was not earlier presented because it is made in response to arguments raised in the final rejection. Entry of the Amendment, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.116, are thus respectfully requested.

I. CLAIM STATUS & AMENDMENTS

As correctly stated in the Office Action, claims 1-19 and 24-29 were pending in this application when last examined. Claims 2-13, 24, and 25 stand withdrawn from consideration as being drawn to a non-elected invention. Claims 1, 14-19, and 26-29 have been examined on the merits. Claims 14-19 and 25-29 stand rejected.

Applicants acknowledge the Examiner's indication that claim 1 is allowed. See June 26, 2002 Office Action, page 7.

The present Amendment cancels non-elected claims 2-13, 24, and 25 without prejudice or disclaimer as to the canceled subject matter. Applicants reserve the right to file a continuation or divisional application on any subject matter canceled by way of this amendment.

The present Amendment also adds new claims 30-36. Support for new claims can be found in the Specification, at least, at page 12, lines 3-10, and in original claim 1. Thus, no prohibited new matter is believed to have been added by this amendment.

Upon entry of the present Amendment, claims 1-19 and 24-36 will be pending in this application. As requested by the Examiner, Applicants hereby attach a courtesy copy of the pending claims as they would stand upon entry of this Amendment.

Applicants submit that the present Amendment should be entered in that the newly added claims encompass subject matter that was previously searched. In particular, the Examiner has already search the isolated amino acid sequence of SEQ ID NO: 4. Accordingly, the present amendment would not raise new issues or require an additional search.

II. FORMAL MATTERS

A. Information Disclosure Statements

Applicants have yet to receive Examiner-initialed copies of the Information Disclosure Statements ("IDS") filed June 8, 2001 and April 25, 2002. Consequently, Applicants request that the Examiner consider the references cited therein and return an Examiner-initialed copy of each. For the Examiner's convenience, Applicants hereby enclose a copy of each IDS, as well as copies of the Transmittal Letter and post-card receipt that accompanied each IDS.

B. Objections & Rejections Withdrawn

Applicants acknowledge the Examiner's withdrawal of the objection of claims 20-23 under 37 C.F.R. § 1.75(c) in view of the Amendment and Reply filed April 25, 2002.

Applicants acknowledge the Examiner's withdrawal of the rejection of claims 1 and 14-23 under 35 U.S.C. § 101 in view of the arguments set forth in the April 25, 2002 Amendment and Reply. See June 26, 2002 Office Action, page 3. In particular, Applicants note the Examiner's acknowledgment that the point mutation in HBM (locus 171 G to V) causes an increase in bone density in HBM-affected individuals.

C. Claims Free of the Art

Applicants hereby note that the claims appear to be free of the art since the Examiner has not made any rejections over the art.

III. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, "HOW TO USE"

Claims 14-19 and 26-29 remain rejected under 35 U.S.C. § 112, first paragraph, because the Specification allegedly fails to teach one of skill in the art "how to use" the claimed invention. See June 26, 2002 Office Action, pages 3-7.

Applicants note that the Examiner has withdrawn this rejection to the extent that it previously applied to claim 1. Applicants submit that the rejection should not apply to newly added claims 30-33 for the same reasons it does not apply to claim 1.

As to the remaining claims, Applicants respectfully traverse this rejection for the reasons set forth in the April 25, 2002 Amendment and Reply and for the reasons herein noted below.

Applicants submit that the Specification fully enables the claimed methods of altering bone development and treatment. In this regard, the Specification discloses the results of linkage analysis and mutation analysis that indicate that older individuals carrying the HBM gene express the HBM protein. As a result of this expression, these individuals do not exhibit the loss of bone mass characteristic with old age. Consequently, these HBM carriers are not susceptible to diseases characterized by reduced bone density, such as osteoporosis. Specification, page 9, lines 21-26, page 31, lines 19-21. Applicants submit that such individuals are equivalent to individuals being treated with the HBM protein. Specification, page 86, lines 20-21. The results also indicate that the HBM affected individuals seem to be resistant to fractures. Specification, page 31, lines 5-10.

The Specification points out that osteoporosis is generally recognized as a disease resulting from a loss of bone mass. For example, the decreased bone formation in patients with osteoporosis-pseudoglioma syndrome results in a low bone mass which makes such patients more susceptible to fractures. Since the Specification teaches that the HBM protein elevates bone mass, it follows that the administration of the HBM protein would alter bone development by elevating bone mass.

Contrary to the assertion made by the Examiner, the Specification provides working examples demonstrating the ability of the HBM protein to alter bone function. In this regard, the Specification provides Northern blot testing and PCR analysis demonstrating

that the protein is expressed in various human bone tissues, such as osteoblasts of the proximal metaphysis, bone marrow, and calvarial bone. See Specification, page 76; Figures 7A & 7B. Table 5 also illustrates that the protein is expressed in proliferating chondrocytes in the growth plate. *In situ* hybridization studies of rat tibia using sense and antisense probes further show that the protein is expressed in various bone tissues. See Figures 10-13. Both the Northern blotting and the *in situ* hybridization reveal a high level of HBM protein expression in bone cells.

To validate and investigate the G171V substitution and the HBM protein as being the cause of the human HBM phenotype, Applicants provide in the Specification the construction of transgenic mice over-expressing the LRP5 G171V mutation in bone. These transgenic animals proved to be viable, healthy, and they exhibited the HBM trait that makes them resistant to bone fracture. See Specification, page 91. More specifically, the LRP5 (G171V) transgenic mice have been shown to possess statistically significant increases in trabecular, and cortical bone parameters resulting in enhancement of femoral and vertebral strength. Thus, these transgenic mice studies provide clear evidence that the protein plays a role in HBM development.

As to the Examiner's assertion that the Specification fails to provide any guidance as to the role of amino acid of SEQ ID NO: 4 (*i.e.*, the HBM protein) in bone development and/or osteoporosis, Applicants submit that this is not required. The Specification need not disclose the HBM protein's effect on any particular cell type, to be effective as claimed, because the Specification makes it clear that HBM affected individuals express the HBM protein and have an elevated bone mass. This elevated bone mass makes the individuals more resistant to fractures. Thus, it follows that such HBM-affected individuals are not susceptible to bone loss diseases such as osteoporosis, regardless of HBM's effect on any particular cell type.

The Specification teaches that HBM is expressed in certain particular cells, such as osteoclasts or osteoblasts. See, e.g., Specification, Figures 10-13. The Specification also makes it clear that the HBM phenotype is the result of altered structure of the protein, as opposed to a loss of a function of Zmax1. In this regard, the Examiner even ***admits*** at

page 3, lines 5-6 of the June 26, 2002 Office Action that "[t]he point mutation present in HBM (locus 171 G to V) causes increase in bone-density in HBM-affected individuals." Thus, in short, one skilled in the art would be able to use the claimed HBM protein to alter bone development, even if the exact function of the protein has yet to be fully elucidated. Therefore, all the Applicants need to show is that HBM alters bone development.

Nonetheless, as even further evidence of the role of HBM in bone development, Applicants further submit the following references:

- Kato *et al.*, *Cbfa1-independent decrease in osteoblast proliferation, osteopenia, and persistent embryonic eye vascularization in mice deficient in Lrp5, a Wnt coreceptor*, J. CELL BIOLOGY 157(2): 303-314 (2002) ("Kim").
- Boyden *et al.*, *High Bone Density Due to a Mutation in LDL-Receptor-Related Protein 5*, THE NEW ENGLAND J. OF MED. 346(2): 1513-1521 (2002) ("Boyden").

While these references were published after Applicants' priority date, these references further demonstrate the use of the HBM protein as described in the instant application.

Kato describes studies in mice that have shown that osteoblast proliferation and function are decreased in the absence of LRP5. In particular, Kato teaches that the LRP5 is expressed in osteoblasts and is required for optimal Wnt signaling in osteoblasts. In this regard, LRP5 regulates bone development by functioning as a Wnt coreceptor. Kato, page 303, Abstract.

Boyden also describes studies demonstrating the ability of the LRP5 to function as a Wnt coreceptor and that the $LRP5_{V171}$ mutation increases bone mass by increasing Wnt signaling. Boyden, page 1513, Abstract; page 1518, second column, third and fourth paragraphs.

Taken together, these teachings further illustrate that the Specification is fully enabled for the use of the HBM protein to alter bone development. As the Specification describes, the HBM gene and the HBM protein are responsible for the HBM phenotype, and are important in bone mineralization and development. Given the evidence that the

HBM protein alters bone development, one skilled in the art would be able without undue experimentation to use the HBM protein to alter such bone development.

The Examiner further argues that Specification is not enabled for altering bone development, because the HBM protein is related to the low density lipoprotein receptor that was previously known to only play a key role in the hepatic clearance of cholesterol carrying LDL. See June 26, 2002 Office Action, pages 4-5. However, Applicants once again submit that any similarity between HBM and LRP5 **does not** negate the evidence provided in the Specification that individuals expressing HBM are protected from diseases, such as osteoporosis. No evidence has been provided as to why HBM's close similarity to LRP5 would eliminate the role of HBM in bone development. If anything, this only suggests the surprising and unexpected findings of the claimed invention.

As to the Examiner's argument that the Specification lacks a working example demonstrating treatment, Applicants submit that it is well established that compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether a working example is disclosed. Instead, the specification need not contain an example, if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without undue experimentation. *In re* Borkowski, 422 F.2d 904, 908, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970); M.P.E.P. § 2164.02. Nonetheless, Applicants submit that the evidence (i.e., familial data, antisense data, transgenic animal studies, *in situ* hybridization studies, etc.) makes clear that the HBM protein elevates bone mass, and thus protects individuals from bone-related diseases. No scientific evidence has been submitted by the Office to demonstrate to the contrary.

In addition, a Specification need not specify the dosage or method of use if it is known that one skilled in the art could obtain such information without undue experimentation. For instance, one of skill in the art would be able to discern an appropriate dosage or method of use without undue experimentation based on knowledge of compounds having similar physiological or biological activity. M.P.E.P. § 2164.01(c). In the instant case, the Specification discloses other treatments for osteoporosis, such as estrogen replacement therapy (*e.g.*, raloxifene and tamoxifene). Accordingly, in light of

these other therapies, one of skill in the art would be able to ascertain the appropriate dosages without undue experimentation. Therefore, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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Date: October 28, 2002

ATTACHMENT TO AMENDMENT AND REPLY

Clean Copy of Pending Claims 1, 14-19, and 26-36 Upon Entry of the Present Amendment

1. An isolated amino acid sequence of SEQ ID NO: 4.

14. A method of altering bone development in a host comprising administering the amino acid sequence of claim 1 to a somatic cell of a host suffering from a bone development disorder.

15. The method of claim 14, wherein the host is a human or another vertebrate.

16. A method of altering bone development in a host comprising administering the amino acid sequence of claim 1 to a germ-line cell in a host suffering from a bone development disorder.

17. The method of claim 16, wherein the animal is a human or another vertebrate.

18. A method of treating osteoporosis comprising administering the amino acid sequence of claim 1 to a patient in need thereof.

19. The method of claim 18, wherein the patient is a human or another vertebrate.

26. A method of treating osteoporosis comprising administering the extracellular domain of an isolated amino acid sequence of SEQ ID NO: 4 to a patient in need thereof.

ATTACHMENT TO AMENDMENT AND REPLY

Clean Copy of Pending Claims 1, 14-19, and 26-36 Upon Entry of the Present Amendment

27. The method of claim 26, wherein the patient is a human or another vertebrate.

28. A method of treating osteoporosis comprising administering the intracellular domain of an isolated amino acid sequence of SEQ ID NO: 1 to a patient in need thereof.

29. The method of claim 28, wherein the patient is a human or another vertebrate.

30. (Newly Added) An isolated amino acid sequence consisting of the amino acid sequence of SEQ ID NO: 4 or a biologically active bone modulating fragment thereof.

31. (Newly Added) The isolated amino acid sequence of claim 30, wherein said amino acid amino contains a glycine to valine substitution at position 171.

32. (Newly Added) An isolated amino acid sequence consisting of the extracellular domain of the amino acid of SEQ ID NO: 4.

33. (Newly The isolated amino acid sequence of claim 32, wherein said amino acid amino contains a glycine to valine substitution at position 171.

34. (Newly Added) An isolated amino acid sequence comprising the amino acid sequence of SEQ ID NO: 4.

ATTACHMENT TO AMENDMENT AND REPLY

Clean Copy of Pending Claims 1, 14-19, and 26-36 Upon Entry of the Present Amendment

35. (Newly Added) An isolated amino acid sequence comprising the extracellular domain of the amino acid of SEQ ID NO: 4 or a biologically active bone modulating fragment thereof.

36. (Newly Added) The isolated amino acid sequence of claim 35, wherein said amino acid amino contains a glycine to valine substitution at position 171.